MULTIPLE SCLEROSIS: ITS OCCURRENCE AND ETIOLOGY.*[1]

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The neurological clinic of Dr. M. Allen Starr was opened in May, 1888. From that time to January 1, 1904, 16 years, there have been received 31,502 patients suffering from some form of nervous or mental trouble. As shown in a report of the clinic for 1903,[2] the percentage of nervous and mental diseases to the entire clinic population—666,226—over these years varied from four to five per cent., in 1890 being as low as 3.6; in 1896 as high as 5.2 per cent. The details showing as follows:

YEAR.	DISEASES OF TOTAL CLINIC.	ALL DISEASES SCLEROSIS.	PROPORTION.
1888 (7 mos.)	732	13,330	5.5%
1889	1,273	29,723	4.3
1890	1,466	34,690	3.6
1891	1,677	35,715	4.7
1892	1,586	35,657	4.4
1893	1.897	39,569	4.8
1894	2,165	41,871	5.1
1895	2,402	46,444	5.1
1896	2,948	54,667	5.2
1897	2,567	51,413	4.9
1898	2,153	48,566	4.5
1899	2,052	48,742	4.2
1900	2,125	48,967	4.3
1901	2,223	47,156	4.7
1902	2,205	45,338	4.8
1903	2,006	44,378	4.5
16 years	31,502	666,226	4.7

INCIDENCE.

During this time there have been recorded in the history books by one or another of the clinical assistants histories of

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*This paper is based upon the material of the clinic of Dr. M. Allen Starr, at the Vanderbilt Clinic, to whom I am indebted for the privilege of making these studies. The work was begun with Dr. A. B. Bonar, with whom an exhaustive analysis of 61 cases was prepared. The extra patients have come to the clinic since 1899.

[1] Read before the New York Neurological Society, June, 1904.

[2] "Dispensary Work in Nervous and Mental Diseases," 1903. By Smith Ely Jelliffe, Journal of Nervous and Mental Disease, Vol. 31, May, 1904, page 309.

109 patients who have been thought to have the symptom-complex held to be diagnostic of multiple sclerosis. Of this number 60 positive cases have been seen by the writer, or by Dr. A. B. Bonar, with whom the present study was begun. It was at first thought possible to trace all the patients and verify or correct the diagnoses, but this was found so annoying and time-consuming by reason of the very migratory propensities of our clinic population (one patient having moved nine times in one year), that after six months of such endeavor it was abandoned.

It has therefore been believed in the present statistical inquiry that the observer who made the records had good and sufficient reasons for making his diagnosis, and save in some instances, in which the recorded data are grossly inadequate, it has been assumed that the diagnosis is as good as other diagnoses made under similar conditions in other clinics, and therefore fit for purposes of comparison. When it is further borne in mind that the multiple sclerosis syndrome is not always clearly cut as a clinical entity the present course seems justifiable. At the same time a certain justification seems necessary in view of the different interpretation placed upon the diagnosis of this condition. It may be stated, however, that no diagnosis of multiple sclerosis was made without the presence of at least three of the four cardinal symptoms, increased reflexes, intention tremor, nystagmus and scanning speech.

If it is assumed that these 109 patients had this disease—or had the symptoms—apart from the pathological limitations hedging about a certain central type of disease,—the incidence of this disease in this clinic to all other neurological cases is .0034 per cent. or about 1 in 300. A comparison of these figures with those recently given in this Society in a discussion on multiple sclerosis, February 4, 1902,[3] may not be without interest. In this impromptu discussion Dana reported ten in three thousand in private practice, and in the twelve thousand general cases at Bellevue one sees only one or two each year. No details over an extended number of years were given, however. In 10,000 cases Dr. Hammond reported as follows: In three thousand private cases he had observed fifteen cases of multiple sclerosis, or ½ of one per cent. (not two per cent. as reported in the JOURNAL.) In 2,400 clinic cases 32 were found, or .008 per cent. In the combined 10,000 cases, 47 had multiple sclerosis, or about .005, one-half of one per cent. Dr. Goodhard reports 27 cases in 10,000 cases from Dr. Starr's clinic,—but inasmuch as Dr. Bonar and myself had up to 1899, 61 possible cases on record of which 32 had been personally examined and verified, these figures are not complete. Dr. Goodhard tells me he rejected all those cases that did not show all the so-called signs of multiple sclerosis, and further he did not go over all of the records. Dr. Sachs had found 13 cases in 2,000 of private record, or 1 in about 135. Dr. Fisher had seen in 2451 cases, eight of multiple sclerosis, or 1 in 306. Dr. Collins reported 46 cases in 9,508 patients, or about one-half of one per cent. Dr. Fraenkel reported in 1,050 cases, 18 cases of multiple sclerosis, or a proportion of 1.7 per cent. His figures are largely taken from a service that represents practically only the terminal nervous complaints, hence his proportion is higher than others who have drawn their figures from dispensary material.

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[3] Journal of Nervous and Mental Disease, Vol. 29, 1902, pp. 284-290.

Dr. Bryon Bramwell[4] has concluded from these figures that multiple sclerosis is much more common in England than in America, his proportion in 5,825 cases being 100, or about 1.7 per cent., one in 59. R. T. Williamson[5] has shown in 2,294 cases of nervous disease at the Manchester Royal Infirmary in ten years, there were 61 patients with multiple sclerosis, a proportion of 2.2 per cent. This is the highest percentage recorded in any records that have been available.

Certainly our own figures would justify Dr. Bramwell's assertion that multiple sclerosis is more common in England than in the United States, and it seems reasonably certain that we make a diagnosis of the disease on much the same lines as our English confrères. If this is true, the cause for this disparity is well worth investigating, in view of the as yet unsettled notions concerning the origin of this disease in general.

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[4] Review of Neurology and Psychiatry, Vol. I., 1903, page 12.
[5] Medical Chronicle, January, 1902.

A comparison with the figures of Jolly's Polyclinic service at Berlin as reported by Seiffer and Laehr may be used as a basis for the comparison of incidence as seen in Germany. The figures for 6 years alone are available.

1896—1897 (6 mos.)	500	6	1.2 %
1897—1898	1,052	10	.95
1898—1899	1,141	13	1.1
1899—1900	1,224	8	.69
1900—1901	1,288	14	1.1
1901—1902	1,774	8	.43
	6,979	59	.84

These figures show an average of .84%, or 1 in every 118 patients affected with general nervous disorders. This is a figure double our figure and half that of Bramwell's.

Saenger's Poliklinik in Hamburg[6] shows the following:

YEAR.	NERVOUS CASES.	MULTIPLE SCLEROSIS.
1893	231	2
1894	319	3
1895	473	5
1896	661	7

Figures for these four years are alone available at this time, but they illustrate a higher percentage than with our clinic patients of this disease.

ETIOLOGY.

It is not the intention of the present study to settle the vexed question of the etiology of this affection. One of our own colleagues, Dr. Sachs,[7] has impressed upon us the fact that unquestionably this disease is protean in origin and that many factors may be instrumental in causing the multiple areas of sclerosis—this is undoubtedly true for clinical multiple sclerosis particularly. Whether we are yet in a position to assert that there is a multiple sclerosis of a classical type, clearly distinguished on pathological grounds from other types, but with similar clinical signs is not for me to discuss, much less decide.

With this outline of the stand taken I would present such facts as have come to our attention which may be construed as bearing in some manner on the question at hand. I am unable at this time to present to your attention a study commensurate with the demands, as has been done by Klausner[8] for the Halle clinic, but some general features may not be considered uninteresting.

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[6] Jahrbücher der Hamburgischen Staatskrankenanstalten.

[7] Critical Digest on Mutiple Sclerosis, JOURNAL OF NERVOUS AND MENTAL DISEASE, Vol. 25, 1898, pp. 314-464.

GENERAL FACTORS: *Sex.*—Charcot first maintained that multiple sclerosis was more frequent in women than in men, but most modern writers are unable to show any marked difference in the incidence of the disease in the two sexes. In our clinic statistics, 68 were male, 41 female. Although the percentage is not particularly marked it seems that in the reports of those observers who have reported a large number of cases that the males slightly preponderate. Thus

Nolda in 26 cases has 16 men and 10 women.

Krafft-Ebing in 100 cases has 58 men and 42 women.

Redlich in 23 cases has 12 men and 11 women.

Stieglitz in 35 cases has 17 men and 17 women—1 (child).

Sachs in 15 cases has 10 men and 5 women.

Lent in 51 cases has 37 men and 14 women.

Blumreich and Jacoby in 29 cases have 23 men and 6 women.

Moran in 8 cases has 4 men and 4 women.

Latsch in 45 cases has 30 men and 15 women.

Hoffmann in 100 cases has 53 men and 47 women.

Klausner in 126 cases has 78 men and 48 women.

Jelliffe in 109 cases has 68 men and 41 women.

Berlin is the only author in whose report women preponderate; in his 39 cases there were 13 men and 26 women. A close study of his paper does not reveal the reason.

It may then probably be taken as established that sex plays little part in the etiology of this affection. There is as Hoffmann asserts, a tendency of the disease to attack healthy men in the early prime of life, but the underlying causes are evidentally those to which both sexes are equally exposed. Yet my own series, and even more, Klausner's figures show a distinct preponderance of the male sex.

Nationality.—In view of the cosmopolitan character of the American population, particularly in a large city such as New York, a note concerning the nationality of our patients may be of interest. Of the 109 patients, 47, less than one-half, were of American birth, and even among these at least 12 were of the second generation of foreign stock. The records indicate the following, United States 47, Germany 20, British Isles 19, 17 being Irish, Austria 6, Sweden and Norway 5, Russia 4, Cuba, Italy and colored each 1, unknown or untraceable 4.

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[8] Arch. f. Psych., 34, 1901, p. 841.

Age.—Concerning the influence of age a large number of studies have brought about considerable modification of standpoints. It was early held that this disease was one of adult life. Later Charcot placed the lower limit at 14 years. It was soon shown, however, by Leyden and later by a large number of others, that early infancy is not exempt, and in late years some observers have come to feel that the disease is one distinctly of youth, although the adult and even the old, are not free.

In the present instance my own figures show that the youngest patient was 4 years of age, and it is not at all unlikely that of the 9 patients under the age of ten in this series, in at least three the disease began in the early days of infancy. The oldest patient was 68 years of age, the disease having been present 4 or 5 years as far as could be ascertained. Crocq has reported a case occurring in a woman of 81; certain difficulties in diagnosis, however, were present.

Tabulated the age incidence in the present series, is about as follows:

AGE.	MALES.	FEMALES.	TOTAL.
0—10	3	6	9
10—20	5	3	8
20—30	14	7	21
30—40	18	9	27
40—50	13	7	20
50—60	12	7	19
60—70	1	0	0
No age obtained			4
			109

Klausner's recent figures show a somewhat similar series: 0 — 10: 4; 10 — 20: 17; 20 — 30, 38; 30 — 40, 36; 40 — 50, 17; 50 — 60, 7; over 60, 2. The younger ages show a slightly higher percentage.

Hoffmann[9] in a recent study has said that the vast majority of his 100 cases occurred between the ages of 18 and 35. In my own series 31 men and 15 women, or 46 in all, less than one-half, would come within these limits; 17, 8 males and 9 females were younger; 43, 27 men and 16 women, were over 35 years of age.

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[9] "Die multiple Sklerose des Centralnervensystems," Deutsche Zeitschrift, f. Nervenheilkunde, 21, 1902, p. 1.

About 8 per cent. of the present series occurred in patients under the age of 10. This is a comparatively high percentage when Bourneville states that in 20 years at the Bicêtre he has observed only four children with multiple sclerosis. Still it is being recognized that the disease is definitely present in infancy; Stieglitz[10] having called attention to the condition, and Schupfer,[11] in the most recent analysis of this disease in infancy, finds reports of at least 59 confirmed by pathological findings. In view of the extreme difficulties of diagnosis of this condition from meningeal and diplegial conditions and from a number of the hereditary developmental diseases, Friedreich's and Marie's ataxia, and others, these figures cannot be considered to be unimpeachable.

It may be worth while to call attention to the high percentage of adults suffering from the disease in this series.

Occupation.—Our own statistics bear out those of practically every worker in this field that the type of occupation plays no important rôle. Hoffmann has well said that often the particular type of clientele of a hospital or clinic seems to show a certain preponderance of one type of occupation, but this is more a matter of locale than anything else. Thus in his own studies he has found a large number of farm workers among his cases, at least 37, but to conclude that work in the garden or field was a predisposing or contributory factor would be nonsense. In the same manner for a city community like New York it would be natural to suppose that a large proportion of the patients would be skilled laborers, or city workers, since such represent a high proportion of our working classes.

Our own figures show that 63 patients were distributed as follows: leather cutter, 2; machinist, 3; glazier, 1; watchman, 1; clerk, 2; tailor, 3; carpenter, 7; painter, 3; brushmaker, 1; driver, 5; servant, 2; porter, 1; insurance agent, 1; theatre manager, 1; actor, 1; electrician, 1; bartender, 1; book-keeper, 1; book-binder, 2; collector, 2; butcher, 2; tanner, 1; engineer, 1; pilot, 1; fish-dealer, 1; seamstress, 1; stable-man, 1; motorman, 1; laundress, 1; shoemaker, 2; waiter, 1; domestic, 4; laborer, 6; housewife, 7; no occupation, 13; the occupations of the remaining were unknown.

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[10] JOURNAL OF NERVOUS AND MENTAL DISEASE, 24, 1897, p. 174. Also American Journal Medical Science, 115, 1898, p. 146.

[11] Monatschrift f. Neurologie u. Psychiatrie, 12, 1902, p. 60.

It therefore seems highly probable that the type of work in which one is engaged bears no relation to the development of the disease.

Heredity.—In Klausner's series, 31 patients showed the effects of some form of inheritance. This is a far higher percentage than any other author has shown. Our own series shows only 8 patients with distinct nervous inheritance. In one the father suffered from traumatic insanity, in another a sister had paralysis agitans, one had an alcoholic father, in two the mother had a tremor; in one, the mother had the same disease; in one, a sister had a marked tremor, and in one the mother had epilepsy. In 21 it is positive that there was no nervous history for two antecedent generations; for the greater number, however, no history was obtainable.

DIRECT CAUSATION.—Turning to a more active phase of the question, what facts, if any, can be obtained from our cases bearing on actual factors. From time to time certain factors have been assumed to be of importance in the etiology of this affection. Trauma, poisoning, acute infectious diseases, any cause lowering the power of an hereditary endowment, any abiatrophy, have each in turn been assumed to play a dominant rôle in multiple sclerosis.

Of these factors it seems probable that three at least are worth inquiring into, acute infectious disease, trauma, poisoning.

Infectious Diseases.—I think we are in a position at the present time to state with definiteness that acute infectious diseases are important etiological factors in this affection. We are also in the position to correct the extreme attitude that it is the only factor—a position which some writers—controversially inclined—assumed was the position taken by Marie.

There is much conclusive testimony as to the relation of infectious diseases to multiple sclerosis in a large number of recent studies. One paper in particular, it seems to me, is deserving of notice inasmuch as it seems to have been entirely overlooked by recent German and English writers. It is a study of Le Brun[12] which is extremely exhaustive and is worthy of special consideration in view of its philosophic mode of handling. Le Brun demonstrates from a wide survey of literature, from personal observations and pathological data that (1) the adjuvant, predisposing causes are the general and local modifications of the environment. Such create the surménage, the emotions, exposure to cold, to traumatism, whereas (2) the acute factor is infection. He cites 120 observations in which the causal relation is thus shown.

German authors have opposed Marie's contention, particularly Krafft-Ebing and Redlich, but at the present time the position taken by Hoffmann is probably the more correct one—that infection undoubtedly plays an important rôle—its influence is undeniable, but other factors are equally important. In 5 per cent. of his cases acute infections played an unquestioned part. Hoffmann calls attention to a common sense feature in this regard, that one should not accept any infectious disease as a factor unless there is a close time relationship between the infection and the onset of multiple sclerosis. In Klausner's figures in 21 patients there was a like relationship shown—in 8 the disease beginning directly after the infection. Typhoid, malaria, rheumatism, smallpox and pneumonia have been the infections most commonly reported on, while in Le Brun's list, measles, erysipelas, diphtheria, scarlet fever, pertussis and syphilis are less frequently represented. Sachs'[13] statement that if infectious disease were the chief cause of multiple sclerosis the vast majority of cases should come on before the age of 15, and also Hoffmann's, loses somewhat of its force when it is remembered how wide the term infectious diseases has grown. Moreover our ignorance of what the chief children's diseases, measles, scarlet fever, really are, should be borne in mind.

Our own figures are not very convincing in regard to infections, for in about 50 per cent. of the cases the observer made no note of having inquired into the subject. In 14 of the remaining 55 patients there was a distinct history of antecedent infectious disease. It is striking that 5 of these patients had malaria. Syphilis was found in 2, tuberculosis in 1, acute articular rheumatism 1, erysipelas 1, influenza 1, diphtheria 1, pneumonia 1, and one unknown febrile affection.

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[12] Archives médicales Belges, 4, 1894, p. 575.

[13] JOURNAL OF NERVOUS AND MENTAL DISEASE, 1898, p. 467.

It will be noted that syphilis is included in this series. Syphilis is considered by most of those observers who have written on the subject to play no rôle whatever. Hoffmann is positive on this point, but admits that multiple syphilitic affections may be clinically indistinguishable, while anatomically distinct. There is a tendency, however, with a number of later students not to reject syphilis entirely—and some excellent observers, Schupfer in particular, ascribe to hereditary syphilis a place in the etiology of this disease, especially in children.

Trauma.—Closely related to infection, if not integrally related with it, is the subject of trauma, first brought into prominence by Leuba and corroborated by Fürstner, Gerhardt, Mendel, V. Jacksch and others. In addition to the testimony of these earlier records Hoffmann gives ten per cent. of his cases as having suffered from trauma, possibly 13; Klausner gives a higher percentage, 26 in his 126 cases, while in our own series, trauma was present in 13. The study of the mutual relations of trauma and infections may bring into prominence these two factors, as associated causes. Such is the lesson of some of the recent work in bacteriology.

Poisons.—Closely related to infection, if not integrally re- our figures are not very convincing. Although three of our patients were painters none of them ever had symptoms of chronic lead poisoning. In view of Oppenheim's figures it is not improbable that lead poisoning may have some importance, but it must be remembered that the locale may be of importance in the determination of this particular factor. Alcoholism was present in a number of Klausner's cases, 8 in our own. Its influence is probably of very minor importance.

Concerning other factors our own statistics show anemia in 2, sexual excesses in 1, epilepsy in 1, business troubles in 1, and in 2 the history of a highly strung nervous condition is recorded.